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Application No.	Ref.	Date
03 778 763.7 - 1211	T 63 001 - oka	11.09.2008
Applicant: NIPPON KAYAKU KABUSHIKI KAISHA		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

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Lange, Tim
Primary Examiner
For the Examining Division

Enclosure(s): 8 page/s reasons (Form 2906)
D5

The examination is being carried out on the **following application documents:**

Description, Pages

1-85 filed with entry into the regional phase before the EPO

Claims, Numbers

1-14 filed with entry into the regional phase before the EPO

1 **Reference** is made to the following documents:

The following document (D1) was cited in the European Search Report

D1: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RAMADAS, SUKURU RAGHU ET AL: "Condensed nitrogen heterocycles derived from indan-1,3-dione" XP002441182 retrieved from STN Database accession no. 1985:95684

The following documents (D2-D4) were cited in the International Search Report

D2: ALTOMARE CASIMO ET AL.: 'Inhibition of monoamine oxidase-B by condensed pyridazines and pyrimidines: Effects of lipophilicity and structure-activity relationships' JOURNAL OF MEDICINAL CHEMISTRY vol. 41, no. 20, 1998, pages 3812 - 3820, XP002976308

D3: NAGARAJAN K., SHAH R.K., SHENOY S.J.: 'Synthesis and reactions of 4,6,7,8-tetrahydro-5(1H)-cinnolinones' INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY vol. 25B, no. 7, 1986, pages 697 - 708, XP002976309

D4: NJOROGE F. GEORGE ET AL.: 'Structure-activity relationship of 3-substituted

N-(pyridinylacetyl)-4-(8-chloro-5,6-dihydro -11H-benzo(5,6)cyclohepta(1,2-b)pyridin-11- ylidene)piperidine inhibitors of farnesyl-protein transferase: design and synthesis of in vivo active antitumor compounds' JOURNAL OF MEDICINAL CHEMISTRY vol. 40, no. 26, 1997, pages 4290 - 4301, XP000992970

The following document (D5) is cited by the Examiner and was found in a further search (see Guidelines C-VI, 8.2 and 8.3). A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D5: US6121266, (VERTEX PHARMA [US],DOLLE ROLAND E [US] ET AL; 14 December 1994 (1994-12-14)

2 **Unity of the invention** (Article 82 and Rule 44 EPC):

2.1 This application was found to be non-unitary, comprising the following three inventions:

a) Compounds of formula (1)
b) Compounds of formula (2)
c) Compounds of formula (1), where J-K-L-M take the value -C(O-Y)=CH-C(W)=CH-.

2.2 A priori, these inventions are united by the broadest common concept of being 3-Phenyl-pyridazine substructure, carrying a -C(=O)-, -CH(OR)- or -C(=NR)- substituent in 5-position, and this substructure having antitumor activity. However, this technical feature has already been disclosed in D5 and the broadest common concept holding together the inventions is thus no contribution over the prior art. Consequently, there arises a lack of unity. Reference is also made to point 3.2-3.3 (lack of clarity of claim 1).

2.3 The document D1 discloses with 3-Phenyl-5H-Indeno[1,2-c]pyridazin-5-one an additional compounds featuring the substructure fragment declared as the broadest common concept between the inventions. Furthermore, D1 discloses this substructure possessing antineoplastic activity, thus presenting this fragment as solving the same problem as the present application. Consequently, D1 is an additional document to support the non-unity of the application.

3 **Clarity of the claims** (Article 84 and Rule 43 EPC)

3.1 Claim 1 is not clear, because the applicant claims "An antitumor agent comprising...an analogue ...of formula (1) or (2)".

3.1.1 As a consequence of this wording, this claim suggests, that the applicant is *not seeking protection for compounds* falling under the formula (1) or (2), that are *not active* against tumors. If this is so, then the application is not solving the problem over the entire breadth of the claim and hence is lacking an inventive step.

3.1.2 However, if the applicant is seeking protection for compounds falling under the general formula (1) and (2), the antitumor activity becomes a mere description, but is not a feature of the claim. However, it is understood, that the claimed compounds are intended for medical purposes.

3.1.3 If the applicant desired to have this feature in the claim, and since the claimed compounds are not novel (see point 4.1) a second medical use type formulation like e.g. "a compound of formula (1) or (2) for use against tumors" would be appropriate (see "second medical use claim", Guidelines C-IV, 4.8).

3.1.4 For the purpose this communication, the examiner adopted the opinion of point 3.1.2. However, the applicant is requested to specify, what formulation for this claim is ultimately intended.

3.2 Claim 1 of the present application is not clear, because of the definition of the variable "J". This variable can take the value "A-C-B", and it remains unclear, how this string of variables integrates into the general formula (1) compound.

3.2.1 It remains unclear, if "A-C-B" is meant to integrate into the bicyclic structure, forming the macrocycle "Pyridazine-A-C-B-K-L-M-pyridazine"

3.2.2 Alternatively, "A-C-B" could be interpreted as forming a macrocyclic ring, with "A" being part of the bicyclic core structure, and "C-B" standing away from the cycle.

3.2.3 Another possibility would be, that "C" is part of the bicyclic core structure, and "A" and "B" stand away from the cycle.

3.2.4 Finally, even "B" could be part of the bicyclic core, and "A-C" stand away from the cycle.

3.3 A similar objection on lack of clarity applies to the definition of the variable "L" in claim 1. Claim 1 states, that "L" can take the value "N-W" or "W-C-W". It is not clear how these fragments are attached to the core structure. The ambiguity illustrated under point 3.2 on how to integrate this variable string into the bicyclic core applies here likewise.

3.4 The examples of the description cast doubt on how to interpreted the claims, since formulas (1) and (2) seem to suggest, that the variable "L" is a divalent fragment, whereas the description lists examples of the variable "L" taking monovalent values (see description, page 17, examples 2,3,4,5.

3.5 Claim 1 is not clear, because it is ambiguous, what lines 17-18 refer to, where it is stated, that "Y and W have the same meanings hereinabove". This could either mean, that "Y" and "W" may take the same values as defined in lines 5-9 and 11-17 respectively, or this could refer to the formula -C(O-Y)=CH-C(W)=CH- in the preceding line specifying that "Y" and "W" take the same values in this construction.

3.6 The scope of claim 1 is not clear due to the definition of the variable "Y", which may take the value "amino acid residue" and further specifies, that this group "may be protected".

3.6.1 This claim essentially encompasses a large number of compounds, which are defined only by reference to a desired functional activity - "being protected". This activity is that they a resistant under a certain set of conditions, but are easy to remove under other conditions. Since this claim seeks protection for chemical substances and not a process, it remains unclear, under what kind of conditions any group should remain stable and under what kind of other conditions such a group should be removable. The description does not provide support and disclosure within the meaning of Article 84 EPC and, in addition, does not appear to be sufficiently disclosed under Article 83 EPC for any such compound potentially fulfilling the desired function.

3.7 Furthermore, claims 1 and 5 are not clear, because the variable "Y" is specified to also be able to take the value "amino acid residue". It remains unclear, how such a residue shall be connected to the core structure, e.g. via O or N-terminus, or via C^2-connection. In the case of bifunctional amino acids like glutamic acid or lycine even more connectivities are conceivable. Hence, such a formulation is unclear.

3.8 Finally, claims 1-4, 6-9 are not clear, because they describe the subject matter, for which protection is sought, with relative term. Examples for these relative terms being used by the applicant throughout the above listed claims are "lower alkyl", "lower alkoxy", "lower alkylamino" etc.

4 **Novelty** (Article 54 EPC)

4.1 The subject-matter of claims 1 and 14 is not novel within the meaning of Article 54(1) and (2) EPC.

4.1.1 The prior art document D3 discloses: 5,6,7,8-Tetrahydro-5-(1H)-cinnolinones. In particular it discloses compound 2a, 7a, 7c, 8, 16, 18 and the tosylate of compound 7a and the methoxime of 2a, all falling into claim 1. D2 doesn't mention these compounds in the context of the current problem that this application tries to solve.

4.1.2 Taking into account the lack of clarity mentioned under 3.1, and adopting the point of view 3.1.2, these disclosures are novelty destroying.

4.1.3 The prior art document D2 discloses: 3-Phenyl-5,6,7,8-tetrahydro-5-oxo-substituted cinnolines. In particular it discloses compounds 28 and 29, likewise destroying the novelty of claims 1 and 15. Compound 28 can be considered a tautomeric form of a formula (2) compound.

4.2 However, the subject matter of claim 2 and claim 9 is novel, since the compounds defined therein are novel due to the definition of the variable "X", defined as being different from hydrogen, whereas the prior art documents D2-D3 only disclose compounds were "X" corresponds to H. The compounds of claim 6 are novel due to their degree of unsaturation.

4.2.1 Consequently, the claims 2-13 are novel.

4.3 Finally it is noted, that the exemplified compounds of the present application are novel.

5 **Inventive Step** (Article 56 EPC)

5.1 Claims 1 and 14 of the present application do not involve an inventive step within the meaning of Article 56 EPC.

5.1.1 Due to claims 1 and 14 not being novel, these claims do not involve an inventive step either.

5.2 However, claims 2-13 of the present application are meeting the requirements of Article 52(1) EPC because the subject-matter these claims involves an inventive step within the meaning of Article 56 EPC.

5.3 D4 has been identified as the closest prior art. D4 discloses: (5,6-Dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-ylidene)-piperidine for treatment of diseases cancer, thus essentially solving the same problem that the present application addresses.

5.4 The compounds of D4 feature a pentacyclic structure as opposed to the compounds of the present application, which are tri-or tetra-cyclic.

5.5 The technical effect of this difference is unknown.

5.6 In the absence of comparative data, the objective technical question would be to find alternative cancer treating compounds.

5.7 It is not obvious when departing from D4, to arrive at the subject matter of the present application.

5.8 The subject matter of claims 2-13 therefore involves an inventive step.

6 General remarks

6.1 To meet the requirements of Rule 42(1)(b) EPC, the prior art documents D2-D4 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

6.2 General comments on ammendments

6.2.1 Amendments should be made by filing replacement pages. Unnecessary recasting of the description should be avoided. An amended abstract is not required. The applicant should also take account of the requirements of Rule

50(1) EPC. If handwritten amendments are submitted, they should be clearly legible to the printer.

6.2.2 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments made, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed on which these amendments are based (see Guidelines E-II, 1).

6.2.2.1 If the applicant considers it appropriate, these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

6.2.3 When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially

of the introductory portion and of any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).